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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,547	06/28/2001	William R. Wagner	214001-00810-1	6231

7590 11/23/2005

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,547	WAGNER ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/11/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6,13-18,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-5,7-12,19 and 20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' election, without traverse, of Group I(i) (claims 11 and 12) is acknowledged. Election was made without traverse in the reply filed on 10/11/2005.

Applicants' election of covalent bond, ester, and biotin/avidin is acknowledged. Election was made during telephone conversation with Arnold B. Silverman, Eckert Seamans Cherin & Mellott, LLC, on October 31, 2005.

Claims 13-18, 21, and 22 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions. Claim 6 has been withdrawn from further consideration as being drawn to non-elected species.

The linking claims 1-5, 7-9, 19, and 20 present in Groups I, II, and III and 10 present in Groups I(i) and I(ii) will be examined in light of their broadest, reasonable interpretation.

Claims 1-5, 7-12, 19, and 20 are pending.

Claim Rejections - 35 USC § 112 - enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 7-12, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for two-step delivery of a chemical or biological entity to an isolated vascular tissue comprising binding of NHS-biotin, followed by the attachment of a chemical/biological entity-avidin conjugate, does

not reasonably provide enablement for method for the delivery to a tissue or cell surface of a chemical or biological entity comprising binding a molecule to the cell surface, wherein the molecule comprises at least one reactive group and at least one signaling molecule, and attaching the entity to the signaling molecule by means of a recognition molecule, wherein the recognition molecule is specific for the signaling molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Breadth of the Claims

The delivery method is asserted by the as-filed application as being effective to deliver therapeutic or diagnostic agents to the tissue or cell surface. Essentially, the method as claimed, consists of attaching a molecule comprising a signaling molecule and a reactive group to a target tissue or cellular surface and introducing a chemical or biological entity expressing or comprising a recognition molecule to the target surface; the signaling and the recognition molecules bind, thereby attaching the entity to the

target surface. The claims are very broad. The method, as claimed, does not rely on inherent feature present on the targeted surface; the target can be any tissue or cell surface. The molecule to be attached can be any biocompatible molecule comprising any group that will function as signaling molecule and any reactive group that would react under mild conditions with groups on the cell surface. Similarly, the entity to be delivered to the target broadly refers to a very broad genus of therapeutic or diagnostic agent, comprising pharmaceutical agents, vectors, nucleic acid sequences, cells or ultrasound contrasting agents. These are very broad ranges that include compounds with different mechanisms of action and pharmacokinetics, therefore the outcome of using these compounds is unpredictable. As will be shown below, these broad aspects are not enabled for their embraced full scope.

The Nature of the Invention

The nature of the invention is a method of delivery of therapeutic agents to the cell surface. Such invention has use in the art for the treatment of disease, such as cancer or cardiovascular disorders.

However, the nature of such invention is within the broad genera of gene therapy and gene therapy does not generally enable Applicants' invention due to delivery problems. For example, Garnett (Advanced Drug Delivery Reviews, 2001, 53: 171-216) teaches:

> "Macromolecular conjugates behave in an entirely different way to low-molecular weight cytotoxic drugs, the action of both being governed in different ways by their physicochemical properties and the physiology and anatomy of the body at both a tissue and a cellular level. Consequently there are different barriers to delivery of macromolecular pro-drugs that for unconjugated drugs. In some cases these are barriers to delivery that have to be overcome.

> The first barrier to delivery is therefore the endothelium of the vascular system and the basement membrane. Macromolecules do cross the normal vascular endothelium slowly, as evidenced by the appearance of serum proteins in the lymph. However this process is sensitive to molecular weight, higher-molecular weight macromolecules being found at lower concentrations in the extracellular fluid relative to serum, that lower molecular weight macromolecules.
> So, for most normal tissues, higher molecular weight serum proteins such as IgG do not achieve the same concentration in the extracellular medium as they are found in serum.
>
> Once in the extravascular compartment, the macromolecule then needs to diffuse through the extracellular matrix".

Hence, from the nature of the invention, the Artisan would not reasonably predict that any signaling molecule/binding molecule combination could be used to deliver therapeutic entities to a tissue or cell surface.

The State of the Prior Art and the Level of Predictability in the Art/Amount of Experimentation Necessary

The issue is whether or not such a claimed delivery of entities to the tissue or cell surface could have been practiced by a person skilled in the art without undue experimentation, at the time the invention was made. How would one of skill in the art know that any signaling/recognition molecules pair is effective in delivering of any chemical or biological to the surface of any tissue in the body? (see Garnett above)

Moreover, the Applicants contemplate treatment of the vascular tissue by delivery of pharmaceutical entities. The specification discloses that the delivery method does not rely on inherent features present on the targeted surface. The binding molecule can be attached to the cell surface via interaction between the reactive group and amino or hydroxyl groups present on the target surface, thereby modifying that surface. Therefore, the method will deliver the chemical or biological entity to other

cells beside the targeted ones. This nonspecific binding of the pharmacological entities can damage normal cells. For example, one preferred embodiment is the use of NHS-biotin/avidin for delivery of therapeutics to the vascular tissue. Intravascular delivery of NHS-biotin results in biotinylation of endothelial cells, as well as all cell types present in the blood, such as platelets and erythrocytes (Peng et al., Blood, 1994, 83: 161-166, Christian et al., Blood, 1993, 82: 3469-3473). Biotinylation does not alter erythrocyte life span; however, subsequent avidin attachment to the biotinylated erythrocytes induces their lysis by complement activation (Muzykantov et al., FEBS Letters, 1993, 318, 2: 108-112). Therefore, more experimentation would be necessary to establish the effective amounts of biotin/avidin to be used without placing the patient under severe anemic conditions. It is noted that the art provides one example of intravascular delivery using endothelial biotinylation and subsequent avidin-FITC binding (Hoya et al., Drug Delivery, 2001, 8: 215-222). However, the whole process was carried out on kidney arteries, wherein the blood flow through the arteries was completely blocked and wherein the arteries were flushed with saline before biotin and avidin-FITC binding.

Further, Applicants disclose that administration of the molecules to the target can be local and delivery of the entity can be either local or systemic. In this case, a potential barrier is the presence of endogenous biotin in serum, which can block the binding of avidin to the targeted cell/tissue. For example, Hamblett et al. (Bioconjugate Chem, 2002, 13: 588-598) teach:

> "Serum-derived biotin can be also problematic in clinical diagnostic applications. Due to the extremely slow dissociation of the biotin-streptavidin complex, the endogenous biotin can irreversible block the biotin-bonding sites of streptavidin and reduce therapeutic efficacy, as well as reduce sensitivity in diagnostic assays.

Strategies to circumvent the blocking of the biotin-binding sites of streptavidin by endogenous biotin may therefore offer therapeutic advantages."

One of skill in the art would need undue experimentation to know how to achieve effective blocking of endogenous biotin-binding sites of avidin.

The Amount of Direction or Guidance/The Existence of Working Examples

The specification only discloses two working examples: one drawn to binding of NHS-PEG-biotin to endothelial cells in culture followed by delivery of avidin-coated microspheres, the other drawn to binding of NHS-PEG-biotin to isolated arteries, followed by the binding of biotinylated endothelial cells via an avidin bridge. Therefore, the specification as filed is not enabling for the claimed invention because the specification as filed does not teach the applicability of other signaling/recognition molecules pairs for the delivery of a chemical or biological entity to a tissue or cell surface. Therefore, specification as filed does not provide any guidance or evidence that any signaling/recognition molecules pair can be used to deliver entities to the cell/tissue surface, as claimed.

Given the reasons above, the specification would need to describe examples that specifically address the use of each relevant signaling/recognition molecule pair for the targeted delivery of chemical or biological entities to any tissue or cell surface. In conclusion, the presently claimed invention only provides enough of a disclosure to allow for an artisan to use only NHS-biotin and a chemical or biological entity conjugated to avidin in a method to deliver a chemical or biological entity to an isolated

vascular tissue, wherein the blood flow is blocked and the blood removed by flushing before the biotin/avidin administration.

4. Claims 1, 2, and 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

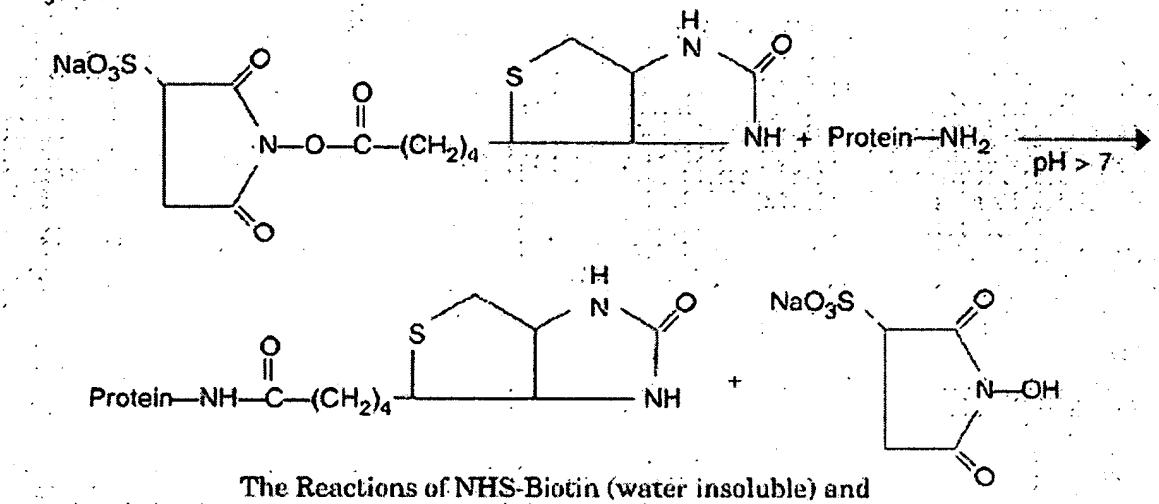
While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The above invention is drawn to a method for delivery to a tissue or cell surface of a chemical or biological entity comprising binding a molecule to the cell surface, wherein the molecule comprises at least one reactive group and at least one signaling molecule, and attaching the entity to the signaling molecule by means of a recognition molecule, wherein the recognition molecule is specific for the signaling molecule and wherein the reactive group is N-hydroxy-succinimide.

However, at the time the invention was made, and even in the present, the art did not teach the feasibility of cell surface attaching of molecules via a N-hydroxy-succinimide reactive group *per se*. Instead, the art teaches the use of N-hydoxy-succinimide esters of biotin for this purpose (Miller et al., Peptides, 1997, 18: 1585-

1595; Muzykantov et al., FEBS Letters, 1993, 318, 2: 108-112, Pierce Biotechnology www/piercenet.com). As shown below, biotinylation takes place by binding of biotin to the primary amines on proteins via its active ester group to form a stable amide bond, while the N-hydroxy-succinimide moiety itself is not involved in the reaction, being released into the reaction medium (Pierce Biotechnology, www/piercenet.com, Avidin-Biotin Chemistry Handbook, page 27).

Figure 3



The Reactions of NHS-Biotin (water insoluble) and Sulfo-NHS-Biotin (water soluble)

Therefore, at the time the instant invention was made, the use of N-hydroxy-succinimide *per se* as a reactive group for binding a molecule to proteins or cell surface proteins was not possible. Given these teachings, the skilled artisan would not know *a priori* how to use N-hydroxy-succinimide *per se* as a reactive group for binding a molecule to cell surface.

It is noted that the specification discloses N-hydroxy-succinimide ester of biotin as a biotinylation reagent for the cell surface. However, the specification does not provide the guidance or the working examples required to overcome the art-recognized

unfeasible use of N-hydroxy-succinimide *per se* for binding any molecule to the cell surface.

Thus, the specification is not enabling for the method of delivery to a tissue or cell surface of a chemical or biological entity comprising binding a signaling molecule to the cell surface via N-hydroxy-succinimide reactive group *per se*, and attaching the entity to the signaling molecule by means of a recognition molecule specific for the signaling molecule, because the delivery of therapeutic agents to the cell surface using N-hydroxy-succinimide *per se* as a reactive group is not possible.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 10, 11, 12, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Saga et al. (Cancer Research, 1994, 54: 2160-2165).

Saga et al. teach in vivo two-step targeting of lung metastases with biotinylated D3 anti-tumor monoclonal antibody (binding molecule that comprises a reactive group that reacts with a specific glycoprotein present on the surface of the tumor cell, i.e., the monoclonal antibody, and a signaling molecule, i.e., biotin) and ^{125}I-labeled streptavidin (recognition molecule specific for the signaling molecule biotin); the delivery is of

pharmaceutical, chemical entity, and chemotherapeutic agent, i.e., ^{125}I (page 2160, Abstract, page 2160, Materials and Methods). Since the art teaches a method of *in vivo* delivery to a cell surface of a chemical entity that is a pharmaceutical and a chemotherapeutic agent, the method comprising (i) binding, to the cell surface, of a molecule that comprises at least one reactive group and at least one signaling molecule, and (ii) attaching the chemical entity to the signaling molecule by means of the recognition molecule that is specific for the signaling molecule, the claimed inventions are anticipated by the above-cited art.

6. Claims 1, 4, 5, 7, 9-11, and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Wojda et al. (Bioconjugate Chem, 1999, 10: 1044-1050).

Wojda et al. teach biotinylation of cell surface with sulfo-NHS ester of biotin (i.e., covalent binding of biotin to the cell surface via a reactive ester bond), followed by DNA-PEI- avidin attachment and endocytosis (i.e., chemical and pharmaceutical entity) (Abstract, page 1045, Experimental Procedures, page 1046, column 2, third and fourth paragraphs, and page 1047, column 1). Since the art teaches (i) a method of delivery to a cell surface of a chemical and pharmaceutical entity, the method comprising covalent binding, to the cell surface, of a molecule consisting of a reactive ester group and N-hydroxysuccinimide and at least one signaling molecule and attaching the chemical entity to the signaling molecule by means of the recognition molecule that is specific for the signaling molecule, and (ii) biotin/avidin as the signaling/binding molecule combination, the claimed inventions are anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 8, 10, 11, 12, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saga et al. (Cancer Research, 1994, 54: 2160-2165), in view of both Francis et al. (International Journal of Hematology, 1998, 68: 1-18) and Kaiser et al. (Bioconjugate Chem., 1997, 8: 545-551).

Saga et al. teach in vivo two-step targeting of lung metastases with biotinylated D3 anti-tumor monoclonal antibody (binding molecule that comprises a reactive group that reacts with a specific glycoprotein present on the surface of the tumor cell, i.e., the monoclonal antibody, and a signaling molecule, i.e., biotin) and ^{125}I-labeled streptavidin (recognition molecule specific for the signaling molecule biotin); the delivery is of pharmaceutical, chemical entity, and chemotherapeutic agent, i.e., ^{125}I (page 2160, Abstract, page 2160, Materials and Methods). Saga et al. do not teach a binding molecule comprising polyethylene glycol (PEG). Francis et al. teach polyethylene glycol (PEG) modification as a well-established technique that has the capacity to solve or ameliorate many of the problems associated with protein pharmaceuticals (page 2, columns 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to PEGylate the binding molecule as taught by Francis et al., with

a reasonable expectation of success. The motivation to do so is provided by Kaiser et al. who teach that, due to their antiadsorptive behavior, PEG chains decrease nonspecific binding (Abstract, page 545, column 2, second paragraph). Thus, the claimed invention was prima facie obvious at the time the invention was made.

8. Claims 1, 10, 11, 12, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saga et al. (Cancer Research, 1994, 54: 2160-2165), in view of both Chinol et al. (British Journal of Hematology, 1998, 78: 189-197) and Wilbur et al. (Bioconjugate Chem, 1996, 7: 689-702).

Saga et al. teach in vivo two-step targeting of lung metastases with biotinylated D3 anti-tumor monoclonal antibody (binding molecule that comprises a reactive group that reacts with a specific glycoprotein present on the surface of the tumor cell, i.e., the monoclonal antibody, and a signaling molecule, i.e., biotin) and ^{125}I-labeled streptavidin (recognition molecule specific for the signaling molecule biotin); the delivery is of pharmaceutical, chemical entity, and chemotherapeutic agent, i.e., ^{125}I (page 2160, Abstract, page 2160, Materials and Methods). Saga et al. do not teach avidin. Chinol et al. teach avidin. Chinol et al. teach that avidin and streptavidin have similar conformations and affinities for biotin (page 189, column 1); however, they have different plasma pharmacokinetics and *in vivo* behaviors, with avidin being rapidly cleared from the circulation (page 189, column 1, first paragraph). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to apply the two-step delivery method of Sato et al. by using ^{125}I-labeled avidin, with a

reasonable expectation of success. The motivation to do so is provided by Chinol et al. who teach that avidin is cleared from the circulation quicker than streptavidin and by Wilbur et al. who teach that longer blood retention of radioactivity can increase non-tumor radiation doses. Thus, the claimed invention was prima facie obvious at the time the invention was made.

Claims 1, 3, 10-12, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saga et al. (Cancer Research, 1994, 54: 2160-2165), in view of Muzykantov et al. (Proc. Natl. Acad. Sci. USA, 1999, 96: 2379-2384).

Saga et al. teach in vivo two-step targeting of lung metastases with biotinylated D3 anti-tumor monoclonal antibody (binding molecule that comprises a reactive group that reacts with a specific glycoprotein present on the surface of the tumor cell, i.e., the monoclonal antibody, and a signaling molecule, i.e., biotin) and ^{125}I-labeled streptavidin (recognition molecule specific for the signaling molecule biotin); the delivery is of pharmaceutical, chemical entity, and chemotherapeutic agent, i.e., ^{125}I (page 2160, Abstract, page 2160, Materials and Methods). Saga et al. do not teach delivery to vascular tissues. Muzykantov et al. teach delivery of a biotinylated anti-PECAM antibody-streptavidin conjugate to pulmonary vascular endothelial cells *in vivo* (page 2382, column 1, last paragraph and column 2, first paragraph). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to apply the two-step delivery method of Sato et al. to deliver biologicial entities to endothelial cells *in vivo* as taught by Muzykantov et al., with a reasonable expectation of success.

The motivation to do so is provided by Muzykantov et al. who teach the biotin/streptavidin system as a valuable tool to targeted delivery of drugs to the endothelium and, potentially, other cell types such as tumor cells or HIV-infected cells (Abstract, page 2379, column 2, fourth paragraph, page 22384, column 1 last paragraph).

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

Ileana Popa